REMARKS

I. Status of the Claims

Claims 1-11, and 14-18, 22, and 24-26 were pending in this application. Withdrawn claims 12, and 27-47 were cancelled without prejudice or disclaimer. Claims 1-3 were amended to further clarify the invention. Support for amendments can be found, for example, in paragraphs [93] to [97]. Accordingly, no new matter has been introduced into the application as a result of the present amendments.

Consideration and entry of this amendment is respectfully requested as it brings the application into condition for an allowance or in better form for consideration on Appeal. Furthermore, the amendments do not raise any new issues that would require further search by the Examiner.

II. Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Simpson

The Examiner further rejects Claims 1-8, 13-17, and 19-26 as allegedly being obvious over Crouch (US 2004/0253658)("Crouch") in view of Simpson et al. (J. Biolum. and Chemilum, 6:97-106, 1991) ("Simpson") Specifically, the Examiner asserts that Crouch teaches a method of detecting kinase activity based on a method that combines a kinase, ATP, and kinase substrate and allowing an enzymatic reaction to occur. By including a luciferase enzyme and luciferin and by measuring bioluminescence of the solution, one can allegedly determine how much ATP was consumed and therefore activity of the kinase can be ascertained. The Examiner admits, however, that Crouch does not teach addition of kinase reaction stopping agents that comprise detergents. To remedy this deficiency, Examiner cites to Simpson who studied the effects of various types of detergents on the kinetics of the luciferase/luciferin reaction. The Examiner lists a number of detergents that Simpson studied which include detergents that do not interfere with luciferase activity and detergents that stimulate luciferase activity. On this basis, the Examiner alleged that it would have been obvious to one skilled in the art to use a secondary solution comprising luciferin, luciferase and a

detergent in a method of detecting transferase activity as described by Crouch. Finally, the Examiner notes that the Applicants' argument to a "single" reagent has not been specified in the claim and that the reagent provided is not necessarily a single reagent, noting that the preferred embodiment requires that the reagent composition is supplied as two components that are admixed before use. Applicants respectfully traverse the rejection.

The invention, as presently claimed, is directed to bioluminescence-based methods for measuring ATP-dependent transferase enzymatic activity. After initiating a transferase reaction, a ***single admixed reagent*** is added to the transferase reaction mixture which simultaneously (a) stops the transferase reaction and (b) initiates the bioluminescence reaction in one step. The single admixed reagent includes a chemostable luciferase, a luminogenic molecule and a detergent. The detergent selectively stops transferase activity without substantially affecting chemostable luciferase activity. See amended claims 1-3. The different constituents in the single admixed reagent may be admixed in any suitable manner to form the single admixed reagent, including admixing of two main components. See the specification at paragraphs [93] to [97].

Crouch

As discussed previously, Crouch merely relates to a method for measuring protein kinase activity which includes: (a) providing a first solution of ATP and protein kinase and a second solution of ATP (control); (b) adding a kinase substrate to the first and second solutions to form reaction mixtures; and (c) measuring ATP or ADP concentration or the rate of change with time based on a bioluminescence reaction. See Abstract of Crouch. A separate secondary stopping agent of phosphoric acid or metal chelators, if used at all, is added to the reaction mixture in step (b') to stop the reaction of the kinase prior to initiation of the bioluminescence reaction. See paragraph [0069].

As correctly pointed out by the Examiner, Crouch does not teach the addition of kinase stopping agents that comprise detergents. See page 5 of the Office action. Furthermore, Crouch is completely ***silent*** about combining a transferase stopping agent with the bioluminescence-generating mixture in a single composition for use in a method

detecting transferase activity as claimed. Indeed, there is no disclosure or suggestion in Crouch of any method that employs a ***single admixed reagent*** which simultaneously stops the kinase reaction and initiates the bioluminescence reaction ***in one step***. A separate stop reagent of phosphoric acid or metal chelators, if used at all, is added to the reaction mixture in step (b') to stop the reaction of the kinase prior to initiation of the bioluminescence reaction. See paragraph [0069]. The use of a separate stop solution demands extra steps to be performed prior to initiating the bioluminescence reaction. See Crouch's Example 1 and paragraph [0102]. See also claims 53 and 55 of Crouch. In fact, not only is Crouch devoid of any teaching or suggestion of combining the steps of quenching transferase reaction and initiating luciferase reaction into one, Crouch declares it advantageous to separate the two actions into two steps. See paragraphs [0069] and [0072]

Moreover, Crouch does not teach the use of a detergent as a stopping agent. Crouch merely relates to the use of EDTA, EGTA or phosphoric acid to stop transferase activity. Contrary to Examiner's assertion, Crouch does not teach or suggest in paragraph [0072] that many compounds, other than EDTA, EGTA, or phosphoric acid, can be used as stopping agent. See page 8 of the Office Action. A general statement in paragraph [0070] that a number of acids such as phosphoric acid can be used as stopping agent, or a single example of using staurosporine does not teach or suggest detergents as stopping agents. Further, there is nothing implicit in the knowledge of one of ordinary skill in the art to modify Crouch's teaching to combine the transferase quenching reagent with the bioluminescence mixture in one solution.

Thus, Crouch does not teach any desirability of the present invention. The present claims would not have been obvious to one of ordinary skill in the art over Crouch with a reasonable expectation of success.

Moreover, Applicants submit that the claimed invention is not obvious over Crouch because Crouch does not teach or suggest all the limitations of independent claims 1-3. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP 2143.03 (*citing In re Royka*, 490 F.2d 981 (CCPA 1974)). Crouch does not teach or suggest a method for detecting transferase activity that employs single regent comprising a detergent and a

luciferase. Crouch does not teach using a detergent as the stopping agent and combining any stopping agent in one solution for quenching transferase and initiating a bioluminescence, nor does Crouch teach a chemostable luciferase. Thus, Crouch does not teach all limitations of the claims. Simpson does not remedy any of the deficiency in Crouch's teachings.

Simpson

Simpson merely relates to the effects of detergents on luciferase activity for low-level detection of microorganisms. Simpson, however, does not teach or suggest using a detergent to stop transferase activity in a single admixed reagent for a method for detecting transferase activity as presently claimed. Simpson may have shown that some types of detergent inhibit luciferase activity, whereas other types of detergent might stimulate luciferase activity within a narrow range of detergent concentrations. See Table 1, and page 102, left column, first paragraph of Simpson. But even among detergents that appear to stimulate luciferase activity, the alleged stimulation is mitigated by the fact that some detergents also irreversibly destabilize and inactivate the luciferase enzyme. See for example, page 102, left column, Table 1, and Figure 2. Thus, Simpson teaches the variability and overall negative effects of detergents on luciferase activities and admonishes:

> Care must be taken in the standardization of firefly luciferase assays when detergents are present. Where such detergents inactivate luciferase during the assay, standardization must be performed in a separate assay (i.e., a known amount of ATP must be added to a separate tube containing the sample prior to addition of the firefly luciferase reaction and that light output from this tube compared with that of a control in which no ATP solution has been added). **At present, it is not practicable to exploit the ability of detergents to increase luciferase reaction rates.** However, the potential exists for reducing the amount of luciferase used in such reagents, as a consequence, reducing assay costs, if the variables can be identified and controlled. [Emphasis added]

See Simpson at page 105 under "Conclusions". Thus, Simpson suggests additional precautionary steps are necessary when dealing with detergents in luciferase reactions

and states that the use of detergents to stimulate luciferase activity is not presently practicable unless variables can be identified and controlled. Simpson, however, does not elaborate on what those variables are and how they can be controlled. A remote "possibility" or mere suggestion to investigate further is no motivation to one of ordinary skill in the art to combine Crouch with Simpson with any reasonable expectation of success. Because of the wide variable effects of detergents on luciferase activity, the need for an additional standardization assay steps when detergents are employed, and the impracticality of using detergents to increase luciferase reaction rates, Simpson can hardly be said to provide any motivation to a person of ordinary skill to use of detergents in luciferase reactions, let alone the use of detergents in a single solution for (a) quenching transferase activity and (a) initiating a bioluminescence reaction in the presently claimed method for detecting transferase activity.

Combination of Crouch and Simpson

Even if Simpson was combined with Crouch, the Examiner's position is untenable. As discussed above, Crouch relates to the use of separate stopping agent in his multi-step method and requires separate steps for: (1) conducting a kinase enzyme reaction; (2) quenching the kinase enzyme reaction, then (3) initiating a luciferase reaction. Thus, Crouch requires the extra step of quenching of the kinase enzyme, followed afterwards with initiating the luciferase reaction.

As discussed above, Simpson merely studied the effect of detergents on luciferase and had shown that detergents have variable effects on luciferase. Simpson is completely silent with respect to quenching transferase enzyme and to a method for measuring transferase enzyme activity based on a single admixed reagent that quenches transferase activity and initiates bioluminescence reaction. There is nothing in Simpson or Crouch that would motivate an ordinary skilled artisan to employ detergent as a transferase stopping agent in the claimed method for detecting transferase activity since neither Simpson nor Crouch teach or suggest the use of detergent as a transferase stopping agent and further the use of detergent in a single solution in a method for detecting transferase activity that simultaneously (a) quenches transferase and (b) initiates transferase activity as claimed.

Assuming arguendo that Simpson teaches the desirability to include detergent in the luciferase reaction solution to enhance luciferase activity as the Examiner would have it, this disclosure is of no moment. The inclusion of Simpson's detergent in Crouch's luciferase solution would not be expected to have any effect on kinase activity simply because kinase activity would have already been quenched by the stopping solution in a prior step. Thus, even if the teachings of Simpson and Crouch were combined, the resulting Simpson-Crouch method still requires the additional stopping step prior to the initiation of the luciferase reaction in a subsequent step. An ordinary skilled artisan would not and could not be motivated by the combined Crouch/Simpson teachings to make and use the presently claimed invention involving the use of a single admixed reagent to simultaneously quench kinase activity and initiate the luciferase reaction with any expectation of success.

Accordingly, withdrawal of the rejection of pending claims 1-8, 14-17, 22, and 24-26 under 35 U.S.C. §103(a) over Crouch in view of Simpson is in order and is respectfully requested.

III. Claim rejection under 35 U.S.C. § 103(a) over Crouch and Simpson and further in view of Briggs

Claims 1-10, 14-17, 22, and 24-26 were rejected under 35 U.S.C. §103 as being unpatentable over Crouch and in view of Simpson and further in view of Briggs et al. (Biochem, 39:489-495, 2000)("Briggs"). Crouch and Simpson has been applied in the same manner as discussed in the above section 103 rejection. Briggs is asserted to support that Src, Lck, Fyn or Lyn are tyrosine kinases. The Examiner alleged that it would have been obvious to one of ordinary skill in the art to use Src Family tyrosine kinases because Crouch and Simpson allegedly teach general utility of their system with kinases generally, and Briggs teaches that the aforementioned proteins are kinases. Applicants respectfully traverse the rejection.

As discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Additionally, Crouch does not teach the use of a detergent as the stopping agent or a chemostable luciferase. Simpson does not

mention transferases and kinases and any method for their detection. Simpson also fails to teach or suggest any transferase stopping agents. Furthermore, as discussed above, the combined teachings of Crouch and Simpson would result in a Simpson-Crouch method that still requires an additional stopping step prior to the initiation of the luciferase reaction in a subsequent step.

Briggs merely relates to additional tyrosine kinase family members. Further, Briggs does not teach or suggest the use of a detergent as stopping agent or any luciferase reaction. As such, Briggs adds nothing to the combined Crouch and Simpson teachings that could remedy the deficiencies. A disclosure of tyrosine kinase family members is not a teaching or suggestion of a method for detecting transferase activity that employs a single admixed reagent that simultaneously quenches a transferase reaction and initiates the bioluminescence enzyme reaction as recited in the present claims. Even if Briggs were combined with Crouch and Simpson, the combined disclosure would result in a Simpson/Crouch/Briggs method that still requires an additional stopping step prior to the initiation of the luciferase reaction in a subsequent step.

The cited art, either alone or in combination, does not teach or suggest the desirability of the invention, nor does it teach every element of the claims. Accordingly, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) based on the combination of Crouch and Briggs is improper and should be withdrawn.

IV. Claim rejection under 35 U.S.C. § 103(a) over Crouch and Simpson in view of Lev

Claims 1-8, 11, 14-17, 22 and 24-26 were rejected under 35 U.S.C. section 103(a) as being unpatentable over Crouch and Simpson and further in view of Lev et al. (EMBO J., 10:647-654, 1991)("Lev") Crouch and Simpson has been applied in the same manner as discussed in the above section 103 rejections. Lev is asserted to support that EGFR, PDGFR, and c-KIT are all receptor tyrosine kinases. The Examiner alleged that it would have been obvious to one of ordinary skill in the art to use growth factor tyrosine kinases because Crouch and Simpson allegedly teach general utility of their system with kinases generally and Lev teaches that the aforementioned proteins are kinases. Applicants respectfully traverse the rejection.

As discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Additionally, Crouch does not teach the use of a detergent as the stopping agent or a chemostable luciferase. Simpson does not mention transferases and kinases and any method for their detection. Simpson also fails to teach or suggest any transferase stopping agents. Furthermore, as discussed above, the combination of the teachings of Crouch and Simpson would result in a Simpson-Crouch method that still requires an additional stopping step prior to the initiation of the luciferase reaction in a subsequent step.

Lev merely relates to additional tyrosine kinase family members. Further, Lev does not teach or suggest the use of a detergent as a stopping agent, or any luciferase reaction. As such, Lev adds nothing to Crouch and Simpson that could remedy the deficiencies in Crouch's and Simpson's teachings. A disclosure of tyrosine kinase family members is not a teaching or suggestion of a method that employs a single admixed reagent that simultaneously quenches a transferase reaction and initiates the bioluminescence enzyme reaction as recited in the present claims. Even if Lev's teachings were combined with the teachings of Crouch and Simpson, combined teachings would result in a Lev/Crouch/Briggs method that still requires an additional stopping step prior to the initiation of the luciferase reaction in a subsequent step.

The cited art, either alone or in combination, does not teach the desirability of the invention, nor does it teach all elements of the claims. Accordingly, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) based on the combination of Crouch and Simpson with Lev is improper and should be withdrawn.

V. Conclusion

The Applicants believe that the application is ready for allowance. A favorable decision is earnestly solicited. If the Examiner has any question, he is invited to call the undersigned attorney.

Respectfully submitted,

Dated: July 1, 2008

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